REMARKS

Status of the Claims

Claims 1-4, 6, and 8-12 have been rejected under 35 U.S.C. 112, second paragraph.

Claims 1-6 and 8-12 have been rejected under 35 U.S.C. 112, first paragraph.

Rejections under Section 112, first paragraph

The Examiner has rejected claims 1-4, 6, and 8-12 under 35 U.S.C. 112 contending that the variables G and *n*, and the ring formed when R^4 and R^5 are combined, are not well-defined. The Examiner also pointed out a misspelling in claim 6. Finally, the Examiner has rejected the definitions of Z and G for lack of written description contending that the variables contain new matter and required cancellation of the new matter with respect to these variables.

In response, Applicants have amended the claims to delete the original groups of Z that the Examiner has contended were indefinite (i.e. where F = alkyl or substituted alkyl), and explicitly set forth the remaining Z groups thereby eliminating diverse definitions for F and the need for new variables T^1 and T^2. Also, the general term "alkyl" has been deleted from the "G" group variable. However, when Z is $C(=O)GR_2$, G includes 1,2 propylene, basis for which is found in species 4 of claim 5. The specification has been amended to reflect the preceding changes.

In addition, Applicants have defined the ring formed when R^4 and R^5 are combined and eliminated multiple uses of the variable "n". The misspelling in claim 6 has also been corrected. Basis for the foregoing amendments can be found in the Examples and original claims. Applicants believe no new matter has been added nor has the scope of the claims been broadened thereby.

Applicants believe all rejections under 35 U.S.C. 112 for indefiniteness and lack of written description have been addressed and request withdrawal of the indefiniteness rejections of claims 1-10 (now claims 1-12).

Rejections under Section 112, second paragraph

The Examiner has also renewed the rejection of claims 1-4, 6 and 8-12 under 35 U.S.C. 112, second paragraph for lack of enablement, contending that the scope of claimed compounds and diseases is too broad for enablement, that the amount of direction provided is useless as it is "completely generic", that there is no biological data presented for any specific compound, that skill in the art is low. Applicants respectfully traverse, first with respect to the compounds (and compositions), covered by claims 1-4 and 6, and second with respect to the method of treatment, covered by claims 8-12.

Compound Claims

Methods for preparing the entire scope of the claimed compounds are addressed in detail on pages 26-34 of the specification. Based upon the instruction found therein, and what is known in the art, one of skill could easily prepare the entire scope of the claimed compounds of the present invention without undue experimentation Accordingly, Applicants request withdrawal of the enablement rejection of claims 1-6.

Method of Treatment Claims

The Examiner still contends that the claimed compounds and diseases are broad and therefore not enabled over the scope of the claims. In response, Applicants assert that scope of the claimed compounds and diseases have been markedly limited by the amendments made to this date and believe that the claims are completely enabled throughout the now significantly narrowed claim scope Additionally, there is sufficient direction in the specification that may be combined with what is known in the art to allow one of skill in the art to treat asthma, rheumatoid arthritis, psoriasis solid organ transplant and COPD.without undue experimentation.

The Examiner took issue with the broadness of the dosage information given in the specification contending that this does not provide enough information to one of skill in the art to practice the invention. Applicants traverse. While the dosage information given in the specification is broad, given this information and the extensive body of literature detailing methods and procedures for determining drug profiles, one of skill can determine correct dosage without undue experimentation.

Presumably in support of his conclusion that little is known in the art, the Examiner observes that certain substituted pyridopyrimidines, which broadly describe Applicants' compounds, have not been used in the art to treat asthma, rheumatoid arthritis, psoriasis solid organ transplant and COPD. In response, Applicants note that it is the fact that Applicants compounds have not been used to treat the aforementioned diseases that makes the present invention patentable. As stated in the specification, and discussed in the last amendment, and demonstrated by the CEM assay there has been ample evidence presented that Applicants' compounds are antagonists of chemokine receptors, particularly CCR4 (specification, pages 1 and 46-48). As discussed previously, as evidenced by the literature, one of skill understands that, antagonists of CCR4 can be useful in the treatment of inflammatory, infectious and immunoregulatory disorders and diseases. Accordingly, the present inventive pyridopyrimidine compounds may be used as therapeutic agents for the treatment of asthma, rheumatoid arthritis, psoriasis solid organ transplant and COPD.

Additionally the Examiner states that the last amendment discussing the biological activity of the compounds was unpersuasive – apparently because

a) It does not state what the particular compound or compounds tested was. There is no way of even knowing whether the compound or compounds

tested were part of the elected invention b) the sentence does not say what this number represent.

The Examiner also takes issue with the range of inhibition over which activity is measured, stating -- without basis -- that "a compound that binds at 100 uM is essentially worthless." and contends that "such a test [presumably the CEM assay] does not establish that the compound is a CCR4 antagonist, it just establishes binding, it could be an agonist for all this test can determine." The Examiner further calls into question the cited activity range saying it is undefined as no units are specified in the application. Applicants traverse.

As discussed previously, the specification, page 48, lines 6-9 clearly states that "the compounds disclosed herein are capable of binding to chemokine receptors at a measurable level". Taken in combination with the "Title" of the application, i.e. ANTAGONISTS OF CHEMOKINE ACTIVITY and the statement on page 1, lines 8 and 9, i.e. "The present invention relates to novel compounds *which are antagonists* of the chemokine receptors . . ." clearly, the inventive compounds disclosed in the specification are antagonists. Moreover, as the compounds demonstrate activity in the CEM assay described in the specification, page 45-48, they are, in particular, antagonists of CCR4. Accordingly, there is ample evidence given in the specification that Applicants' compounds have utility as antagonists of CCR4 activity. To eliminate doubt, claims 8, 9, 10, 11 and 12 have been amended to include this antagonist activity. Finally, one of skill in the art should understand that since the CEM assay utilizes a native cell line, inhibition values are necessarily IC50 values. The specification has been amended to reflect this.

The Examiner also cites, as evidence of low of level of skill in the art, his lack of ability to find what he regards as significant publication supporting the use of CCR4 antagonists as therapeutic agents. He dismisses the references provided in the background as signifying that CCR4 antagonism is "merely an area of research interest", apparently ignoring the fact that many of the references arise from the pharmaceutical industry, clearly a commercial enterprise. Applicants cite the following references (a full copy of which accompany this office action) that support the use of chemokines and their receptors, and CCR4 antagonists in particular, in the treatment of asthma, rheumatoid arthritis, psoriasis solid organ transplant and/or COPD. This list is not comprehensive, and only represents an example of the knowledge of one of skill in the art concerning asthma, rheumatoid arthritis, psoriasis solid organ transplant and COPD at the time of filing the present application.

General references: Campbell, J.J. et al., *J. Immunol.* 163:2353-2357 (1999); and Campbell, J.J. et al., *Nature*, 400:776-780 (1999); Sallusto, F. et al., Eur. *J. Immuno* 29:1617-1625 (1999); and Tang H. L. et al., *Science* 284:819-822 (1999).

Psoriasis: Krueger, *J. Am. Acad. Dermatol*, 46:1-23 (2002)*; Wakugawa M. et al., *Drug New and Perspective* 15(3):175-179 (2002), Campbell et al., *Nature*, 400(19):776-780 (1999), U.S. Patent # 6,245,332; Tang H. L. et al., *Science* 284:819-822 (1999);; *J. Clin. Invest.* 104(8): 1097-1105 (1999); *J. Invest. Dermatol*, 115:640-646 (2000); and *Clin, Exp. Allergy*, 32(8):1236-1242 (2002).
COPD and Asthma: J. Exp. Med. 191(2):265-273 (2000); *Immunol. Rev.* 177:31-42 (2000); *J. Immunol.*, 171(1):11-15 (2003); *Current Opin . In Pharmacol* 3:443-448 (2003); *J Immunol.*, 162:2375-2383 (1999); *Am J. Path*, 165(4):1211-1221 (2004); *J. Immunol,* 163(1):403-411 (1999); *FASEB J.*, 16(10):1313-1315 (2002); *J. Immunol*, 173(7):4692-4698, (2004); and *J. Clin. Invest.* 107(11);1357-1364 (2001).
Rheumatoid Arthritis: *Nature*, 400(19):776-780 (1999); *Arthritis Rheum.*, 44(12):2750-2760 (2001); *J. Immunol.* 166:6899-6906, (2001); *Arthritis and Rheum,* 44(5):1022-1032 (2001).
Solid Organ Transplant: *Eur. J. Immunol*, 32(11):3171-3180 (2002).

*It should be noted that the Examiner cited Krueger's review in his determination that what was known in the art was insignificant stating that the review "provides an extensive review of potential new biological agents, yet CCR4 gets only the briefest passing notice. . . indicating that the skill level in this art is negligible." Applicants note that Krueger is not especially relevant as the present invention is not a biologic, but a small molecule therapeutic. However, Krueger cites many significant references that support the use of small molecule therapeutics in the treatment of psioriasis, referring to the up-regulation of both CCR4 ligands in the psoriatic skin lesions as well as the accumulation of T-cells specifically bearing CCR4.

Given the high level of skill it the industry as evidenced by the aforementioned references, as well as what is given in the background of the Specification, Applicants believe that given what was known in the art, there was enough information was available at the time of filing the present application to allow one of skill in the art to use the present inventive compounds, which are CCR4-antagonists, to treat asthma, rheumatoid arthritis, psoriasis solid organ transplant and COPD.

For at least the reasons discussed above, Applicants assert that, contrary to the Examiner's conclusion, a Wands factor analysis indicates that at the time this specification was filed, one skilled in the art could make and use the full scope of the claimed invention. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. 112, second paragraph for lack of enablement.

Objections

The Examiner has objected to claim 5 contending that claim fails to limit the subject matter of a previous claim. Applicants believe that the present amendments render this objection moot and request withdrawal of the objection.

Summary

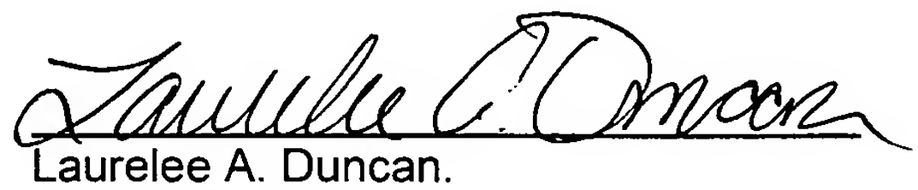
Applicants believe the claims are now in condition for allowance. The Examiner is invited to contact the undersigned by telephone, at the number listed below, if it is believed that a telephonic communication would facilitate the prosecution of this application.

Fees

No additional fees should be due, aside from the fee for the two-month extension of time. However, if it is determined that an additional fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-5323



Laurelee A. Duncan.
Attorney for Applicants
Reg. No. 44,096

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